Editorial

Annals of Oncology 15: 700–701, 2004
DOI: 10.1093/annonc/mdh195

Bisphosphonates and reduction of skeletal events in patients with bone metastatic breast cancer

Formerly called diphosphonates, bisphosphonates have been used as water softeners since the second half of the nineteenth century. Their role in bone and mineral metabolism was recognized about 35 years ago with the pioneering research of Herbert Fleisch in Switzerland [1, 2]. More recently, bisphosphonates have become the first choice for standard care in the management of bone diseases associated with hyper-resorption, such as Paget's bone disease, hypercalcemia of malignancies, osteoporosis (both idiopathic and secondary), disuse, and prosthesis or implant loosening. Their consistent and large efficacy in preventing skeletal events associated with bone metastases is a situation in which bisphosphonate treatment has fundamentally modified the course of the disease complications, and hence has contributed to decreased bone pain, skeletal morbidity and to a markedly improved quality of life for numerous patients [3, 4]. Bone metastases may be present in more than three-quarters of patients with breast cancer. A recent systematic review [4] indicates that bisphosphonate therapy of patients with metastatic breast cancer is associated with: a reduction of non-vertebral fracture [odds ratio (OR) 0.80], combined fractures (OR 0.75), a need for radiotherapy (OR 0.65) or for orthopedic surgery (OR 0.59), and episodes of hypercalcemia (OR 0.43). For metastatic bone diseases, the benefit of bisphosphonates on radiotherapy and hypercalcemia are observed as early as at 6 months, whereas the need for orthopedic surgery is significantly decreased by 24 months. These data clearly illustrate the magnitude of the benefits of bisphosphonate therapy on bone-related morbidity (20% to >50% reduction in skeletal events), and the expected time frame of these benefits. In addition, bisphosphonate therapy significantly increases the time to the first skeletal-related event, but bisphosphonates do not appear to affect overall survival, with the possible exception of some patients subgroups. Their efficacy in reducing breast cancer morbidity has been demonstrated in well-conducted randomized, placebo-controlled trials, with the intravenous administration of pamidronate, zoledronate or ibandronate [5–8], or with clodronate given orally [9, 10]. Oral bisphosphonates appear to be associated with lower ORs for vertebral and non-vertebral fracture risk, somewhat equivalent to the intravenous treatment.

The phosphate–carbon–phosphate structure of bisphosphonates makes them resistant to hydrolytic enzymes and confers a preferential and selective tropism for bone mineral. Thus, they specifically accumulate on the surface of bone. This characteristic represents the basis of bone scintigraphy with technetium-labeled phosphonates. The duration of the effects of bisphosphonate may be related to their binding affinity for hydroxyapatite. Those compounds with a stronger binding appear to have a longer duration of action. Once taken up by the bone osteoclasts during the course of bone resorption, bisphosphonates both reduce osteoclast activity and promote their apoptosis. The molecular mechanism of action involves either the incorporation of bisphosphonates into inactive ATP analogs (this mechanism involves clodronate, etidronate and tiludronate) or the inhibition of the enzyme farnesyl synthase, an enzyme in the cholesterol synthesis pathway (for nitrogen-containing bisphosphonates). The product of this enzymatic reaction, farnesyl-pyrophosphate, or the next product, the lipid geranylgeranyl-pyrophosphate, bind to Ras, Rho and other GTPases, through a reaction called prenylation, which is required for cytoskeletal organization and vesicular traffic within the osteoclasts. Decreased prenylated proteins lead to osteoclast inactivation [11, 12]. Bisphosphonates may also exert direct antitumor activity by decreasing cancer cell proliferation, adhesion to and invasion of extracellular matrix, and metalloproteinase release. However, these effects have been demonstrated mainly *in vitro*.

Although there is no head-to-head comparison between intravenous (i.e. nitrogen-containing bisphosphonates) and oral administrations (mainly clodronate), the better bioavailability of the former (bioavailability of oral bisphosphonates is ~1%), together with potential gastrointestinal side effects, and the risk of insufficient compliance with the latter, support the use of intravenous nitrogen-containing bisphosphonates in the treatment of breast metastatic bone disease [3]. However, this treatment schedule requires regular clinic visits, which can reduce treatment convenience for some patients. In the setting of adjuvant therapy of breast cancer with bisphosphonates [13], or of the long-term prevention of bone loss, oral formulation would offer some advantage and convenience, provided an equivalent efficacy with intravenous administration and minimal side effects could be ensured.

Ibandronate is a newly approved nitrogen-containing bisphosphonate in the European Union, with both intravenous and oral formulations. Its efficacy in preventing skeletal events resulting from metastatic breast cancer have been demonstrated in randomized double-blind, multicenter phase III trials, in which the primary end point was the number of 12-week periods with new skeletal events. The occurrence of vertebral or non-vertebral fractures, radiotherapy or surgery to bone during such a period was expressed as skeletal morbidity period rate. Compared with placebo, intravenous ibandronate administered every 3–4 weeks at a dose of 6 mg significantly reduced the skeletal morbidity period rate by 40%, as assessed in a multivariate Poisson regression analysis [8]. The oral daily form of 50 mg reduced the risk of new bone events by 39% and was apparently well tolerated, as shown in this issue of *Annals of Oncology* by Tripathy et al. [14].

Using a *post hoc* analysis of time to multiple skeletal events, the equivalent efficacy of the two ibandronate formulations was recently confirmed [15]. However, in contrast to other bisphosphonates, oral ibandronate did not appear to reduce vertebral or non-vertebral fracture risk in this 96-week trial. Whether this lack of effect on fracture risk is related to the type of patient investigated, the kind of antitumor regimen administered or to the drug itself, deserves further study. Thus, direct comparative trials with identical end points are needed to compare the reductions in new skeletal events with intravenous and oral formulations of ibandronate, and with other bisphosphonates. The results of such studies should help to determine the place of oral ibandronate in the management of breast cancer patients.

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